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Diverse types of ganglion cell photoreceptors in the mammalian retina

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ABSTRACT

Photoreceptors carry out the first step in vision by capturing light and transducing it into electrical signals. Rod and cone photoreceptors efficiently translate photon capture into electrical signals by light activation of opsin-type photopigments. Until recently, the central dogma was that, for mammals, all phototransduction occurred in rods and cones. However, the recent discovery of a novel photoreceptor type in the inner retina has fundamentally challenged this view. These retinal ganglion cells are intrinsically photosensitive and mediate a broad range of physiological responses such as photoentrainment of the circadian clock, light regulation of sleep, pupillary light reflex, and light suppression of melatonin secretion. Intrinsically photosensitive retinal ganglion cells express melanopsin, a novel opsin-based signaling mechanism reminiscent of that found in invertebrate rhabdomeric photoreceptors. Melanopsin-expressing retinal ganglion cells convey environmental irradiance information directly to brain centers such as the hypothalamus, preoptic nucleus, and lateral geniculate nucleus. Initial studies suggested that these melanopsin-expressing photoreceptors were an anatomically and functionally homogeneous population. However, over the past decade or so, it has become apparent that these photoreceptors are distinguishable as individual subtypes on the basis of their morphology, molecular markers, functional properties, and efferent projections. These results have provided a novel classification scheme with five melanopsin photoreceptor subtypes in the mammalian retina, each presumably with differential input and output properties. In this review, we summarize the evidence for the structural and functional diversity of melanopsin photoreceptor subtypes and current controversies in the field.

Contents

Abbreviations: DA, Dopaminergic amacrine; EGFP, enhanced green fluorescent protein; DAG, diacylglycerol; GCL, ganglion cell layer; Ih, hyperpolarization-activated current; L-AP4, L-2-amino-4-phosphono-butyric acid; IPL, inner plexiform layer; ipRGCs, intrinsically photosensitive retinal ganglion cells; LGN, lateral geniculate nucleus; NIF, non-image-forming; OPN, olivary pretectal nucleus; Opn4, Opsin 4; PLR, pupillary light reflex; PKC, protein kinase C; RGC, retinal ganglion cell; SCN, suprachiasmatic nucleus; TRP, transient receptor potential channel; TRPM, transient receptor potential channel subfamily M; RPE65, RPE specific protein 65 kDa.

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1. Introduction

Retinal ganglion cells (RGCs) in the mammalian retina comprise at least 10–15 types that are classified according to common structural and functional features (Masland, 2011; Wassle, 2004). The most recently discovered RGC type is the intrinsically photosensitive retinal ganglion cell (ipRGC). These ipRGCs, in addition to acting as a conventional RGC, are also bona fide photoreceptors that express the photopigment melanopsin (Opn4), which renders these cells directly sensitive to light. Melanopsin shares a higher degree of amino acid sequence homology with invertebrate opsins than vertebrate opsins. Unlike the conventional rod and cone photoreceptors of the mammalian retina, ipRGCs express the melanopsin photopigment diffusely along the dendrites and soma of the cell, and translate photon capture into spike frequency changes. This allows ipRGCs to directly convey ambient irradiance signals to higher brain centers. Genetic and immunological cell ablation experiments in mice have conclusively demonstrated that ipRGCs are obligatory for so-called non-image-forming (NIF) visual responses including circadian photoentrainment, pupillary light reflex, and light suppression of locomotor activity. ipRGCs have also been implicated in light exacerbation of migraine, photophobias, seasonal affective disorders, and more recently in pattern vision. Advances have been made in the past few years indicating an unforeseen diversity in the structure and function of these novel photoreceptors. Physiology, molecular biology, and behavioral studies have revealed that distinct ipRGC subtypes in mammals respond differentially to light stimulation, project to distinct higher order visual centers, and possibly evoke diverse behaviors. There are three subpopulations of ipRGC based on the stratification of their dendrites in the inner plexiform layer (IPL), those monostratified in the OFF sublamina (M1), those monostratified in the ON sublamina (M2), and those bistratified in both the ON and OFF sublamina (M3) (Schmidt et al., 2008; Viney et al., 2007; Warren et al., 2003). Moreover, two additional subpopulations of ipRGCs (M4 and M5) with particularly low levels of melanopsin expression and dendrites in the ON sublamina of the IPL have recently been uncovered using novel melanopsin reporter mouse lines (Ecker et al., 2010). Many excellent recent reviews have emphasized the mechanisms of phototransduction in ipRGCs and role of these cells in physiology and disease (Bailes and Lucas, 2010; Do and Yau, 2010; Guler et al., 2007; Hankins et al., 2008; Hatori and Panda, 2010; Pickard and Sollars, 2010, 2011; Schmidt et al., 2011). Our review emphasizes the identification of ipRGC subtypes in the mammalian retina and highlights the current knowledge of the morphological and functional diversity of these novel photoreceptors.

1.1. Behavioral responses to light

Organisms have evolved complex mechanisms for detection and adaptation to ambient light levels. In mammals all light detection is performed by two visual pathways, the image-forming and the NIF systems. In contrast to the image-forming visual system, which processes photic signals related to color, contrast and motion, the NIF visual system is primarily engaged in detection of ambient luminance levels. NIF visual responses include the regulation of the circadian clock, regulation of pupil size, and pineal melatonin secretion. One well characterized NIF visual response is the light regulation of internal circadian clock. All living organisms harbor an internal circadian timing system that adjusts many physiological variables to daily environmental light and dark cycles (Panda et al., 2002a; Takahashi et al., 2008). In mammals, circadian behavior is regulated by a neuronal oscillatory network located in the suprachiasmatic nuclei (SCN) of the hypothalamus (Reppert and Weaver, 2002). Although the SCN intrinsic rhythm exhibits near 24 h periodicity (circadian), in the absence of environmental cues it gradually becomes out of phase with the external light–dark cycles. In mammals, this circadian rhythm is primarily adjusted (or entrained) by environmental light–dark cycles. Photoentrainment signals travel through a direct pathway from the retina to the SCN, the retinohypothalamic tract (Hendrickson, 1972; Moore and Lenn, 1972; Moore et al., 1995; Pickard and Silverman, 1981). This photoentrainment is driven by a visual stimulus quite distinct from that conveyed by the conventional visual pathways in that it is relatively insensitive to brief light stimulation or to low light levels (Nelson and Takahashi, 1991). During the photoentrainment process, light depolarizes RGCs, which in turn release glutamate and pituitary adenylate cyclase-activating polypeptide from their axon terminals (Hannibal, 2006). Bilateral enucleation and retinohypothalamic tract lesion studies in rodents have shown that electrical signals transmitted by RGC axons to the SCN are absolutely necessary for circadian photoentrainment (Johnson et al., 1988; Nelson and Zucker, 1981).

Another well-established NIF visual response is the pupillary light reflex (PLR) which regulates the amount of light that reaches the retina across varying levels of environmental illumination. The PLR is the constriction of the sphincter pupillae muscles of the iris in response to an increase in ambient luminance. This light response involves a bilateral projection from the retina to the olivary pretectal nucleus (OPN) which in turn sends fibers to the Edinger-Westphal nucleus. The Edinger-Westphal nucleus contains the autonomic neurons that control pupil size. Furthermore, an autonomous, non-neural PLR component driven by melanopsin phototransduction in the iris muscles of nocturnal rodents has recently been described (Xue et al., 2011). In addition to its roles in photoentrainment and the PLR, light also suppresses pineal melatonin synthesis and secretion in mammals (Lewy et al., 1980; Wurtman et al., 1963), suppresses sleep in diurnal animals and enhances sleep in nocturnal animals (Borbely, 1978; Saper et al., 2005), reduces locomotor activity in nocturnal animals (Borbely, 1978), and enhances activity in diurnal mammals (Redlin, 2001). Finally, NIF visual responses may also be involved in light exacerbation of migraine pain (Noseda et al., 2010) and photophobias (La Morgia et al., 2011).

1.2. From frog melanophores to melanopsin

Studies of NIF visual responses in mice with severe loss of rod/cone function provided the initial evidence for a third photoreceptor type in the inner retina. Mice were described in the early 1920's with an autosomal recessive mutation leading to "the absence of visual cells (rods), the external nuclear layer, and the